Claim 1 (and hence its dependent claims 2-19) recites "a powder of reversed vesicles, which comprises one or more non-ionic surfactants."

Contrary to the assertion of the Office Action, the cited references do not teach or suggest all the claim limitations. EP 0 521 562 teaches a method of preparing reversed vesicles, but does not teach a powder of reversed vesicles. The Office Action asserts that this deficiency can be cured by EP 0 678 295, allegedly by teaching that vesicular preparations can by lyophilized to form powders, referring specifically to pages 14 and 15, examples 34 and 35. The Applicants note, however, that EP 0 678 295 contains no such pages or examples. EP 0 678 295 teaches a complex of phospholipid/active principle (i.e. a mixture of components, not reversed vesicles), wherein such a complex may be a gel, a liquid, or a powder, and wherein such a complex *must be further manipulated in order to form liposomes.* EP 0 678 295 does not teach a powder of reversed vesicles.

The Office Action further asserts that the deficiency in EP 0 521 562 may be cured by EP 0 159 237, alleging that it teaches micelles can be freeze-dried to form powders. Contrary to the assertion of the office action, EP 0 159 237 teaches the lyophilized product of an *emulsion of the oil-in-water type.* An oil-in-water emulsion is a heterogeneous system of a lipid liquid dispersed in an aqueous liquid in the form of droplets, whereby the two liquids are immiscible. This structure is quite different from vesicle-containing dispersions. Hence EP 0 521 562 does not teach a powder of reversed vesicles.

The Office Action additionally asserts that the deficiency in EP 0 521 562 may be cured by GB 2 002 319, alleging that it teaches dehydration of liposomes to prepare a stable powder. GB 2 002 319 does not teach a powder of reversed vesicles but in fact rather *teaches away* from a powder of reversed vesicles. The specification of GB 2 002 319, page one, lines 39 to 43, states:

> "Now, the dehydration operation is, in itself, not sufficient to practically implement the process of the invention and the initial mixing with a hydrophilic compound is a must. Effectively, it has been shown from experiments that the simple dehydration by lyophilisation of the liposome dispersion results in the formation of an oily sticking residue which is practically insoluble in water afterwards and which is thus useless for the reconstitution of a liposome dispersion suitable for usual liposome application."

GB 2 002 319 teaches away from a powder of reversed vesicles and rather teaches a powder of liposomes *with a hydrophilic compound.* Such a hydrophilic compound is not required in the present invention.

The Office Action additionally asserts that the deficiency in EP 0 521 562 may be cured by JP 05 194253, alleging that it teaches a powder of reverse micelles. JP 05 194253 teaches a powder of reverse micelles, not a powder of reversed vesicles. Reversed micelles and reversed vesicles are two distinct entities, with different biological properties. Confirmation of this can be found in *J. Am. Chem. Soc.* (1991) 113:1051 and in Attwood et al. ("Surfactant Systems: Their chemistry, pharmacy and biology," p. 212, Chapman and Hall, London, 1983); copies of both of these documents were supplied by the Applicants with their response to the Office Action Mailed May 29, 2001.

Thus, none of the cited references, either alone or in combination, teach or suggest a powder of reversed vesicles, and as such the cited references do not meet the requirements of a rejection under 35 U.S.C. 103(a) as they fail to teach all the claim limitations.

Furthermore, there is no suggestion or motivation to modify EP 0 521 562 with the teachings of EP 0 678 295, EP 0 159 237, JP 05194253, and GB 2002319. EP 0 687 295, EP 0 159 237, and JP 05194253 teach lyophilization or dehydration of entities other than reversed vesicles, i.e., a complex of phospholipid/active principle, an *emulsion of the oil-in-water type*, or micelles. Such entities are distinct from reversed vesicles, and there is no suggestion within the cited references that the disclosed processes could be extended to reversed vesicles. Additionally, GB 2002319 in fact teaches away from lyophilization of reversed vesicles, as discussed above.

Also, there is no expectation of success proffered by the combination of the cited references. Moreover, GB 2002319 suggests the methodologies employed by the instant invention would not be successful. The instant invention thus shows evidence of unexpected results. "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness..." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985).

Additionally, the instant invention is nonobvious in that the presently claimed powder of reversed vesicles, when dispersed in an apolar vehicle such as a biodegradable oil, retains its vesicular

structure with a yield much greater than when the reversed vesicles are prepared directly in the biodegradable oil. The yield of reversed vesicles prepared directly in biodegradable oil is quite low, where the yield of reversed vesicles prepared in, for example, silicone oil, dried, and reconstituted in a biodegradable oil is much greater. Support for this can be found in the specification on page 2, lines 10-14, on page 4, lines 8-11, and in examples 5-8. Confirmatory data can also be found in *J. Pharm. Sci.* (2000) 89:930-939, a copy of which is enclosed for review by the Examiner. Such a property is nowhere taught, suggested, or contemplated by any of the any of the cited references. MPEP 716.02(a): Presence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesh*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Furthermore, on page 3, final paragraph, the Office Action states:

> "...This argument is not found to be persuasive since a careful examination of the specification indicates that it does not contain any data of the encapsulation before the preparation of the powder which would enable one to determine whether the differences observed are significant or not and unexpected or not..."

The applicants respectfully traverse this assertion. Example 5 of the specification discloses an attempt to create dispersions of reversed vesicles directly in various biodegradable oils and in silicone oil. With the exception of the preparation in silicone oil, the yield of reversed vesicles in these oils was quite low. Thus, the encapsulation efficiency of PABA could not be determined due to a lack of sufficient vesicular material (see page 8, lines 18-19), explaining its absence from the specification.

Furthermore, Example 3 discloses reconstitution of reversed vesicles in various biodegradable oils and in silicone oil from a powder of reversed vesicles prepared by the methods of the present invention, i.e., prepared in silicone oil. This Example clearly demonstrates that vesicular material is present in all biodegradable oils. Example 4 discloses encapsulation efficiency values for PABA in the vesicular systems of Example 3.

In short, no *prima facie* case of obviousness can be established, and furthermore there is evidence of nonobviousness in the unexpected property of the instant invention as recited above. Thus the Applicants respectfully request the Examiner reconsider and withdraw the rejections under 35 U.S.C. 103.

If the Examiner believes that a telephone or personal interview would expedite prosecution of the instant application, the Examiner is invited to call the undersigned attorney at (312) 913-2135.

Respectfully submitted,

Date: August 29, 2002

Michael S. Greenfield
Reg. No. 37,142

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002